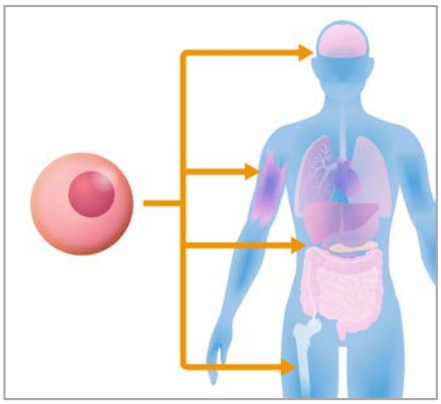
What if we could renew all our cells?

Regenerative medicine (RM) is an interdisciplinary field that applies engineering and life science techniques to restore tissues and organs damaged by age, disease or trauma, as well as those with congenital defects. Promising data indicate that RM could be used across a wide array of organ systems and contexts, including surface wounds, cardiovascular diseases and traumas and treatments for certain types of cancer.

A key principle of RM is the delivery of therapeutic cells that directly contribute to the structure and function of new tissues, which are either autologous (derived from the same individual) or allogeneic (derived from different individuals of the same species). Numerous RM strategies are employed, including the use of materials and newly generated cells to take the place of missing tissue, replace its structure and function, or contribute to tissue healing. The body's innate healing capabilities may also be used to promote regeneration. These strategies can be divided into four broad categories: 1) Recapitulating organ and tissue structure; 2) Integrating grafts with the host via vascularisation and innervation; 3) Altering the host environment through cell infusions or modulating the immune system; 4) Exploiting existing and new cell sources.



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Potential impacts and developments

Recapitulating organ and tissue structure. Tissue and organ architecture is intrinsically connected with their function, therefore the ability to recreate their structure is essential to successfully regenerate the development of (recapitulate) healthy tissue. One such strategy is to decellularise organs, which involves the removal of immunogenic cells and molecules without losing structural and mechanical properties, and to recellularise them before transplantation. This approach has been used in animal models of liver, lung, kidney and other organ diseases. Decellularised tissues, without recellularisation, have been used to repair large muscular defects in humans.

Another approach for recapitulating organs is the fabrication of scaffolds. They can be made from naturally derived materials or from synthetic polymers. For example, hydrogels are composed largely of water and are often used as scaffolds due to their compositional similarity to tissue. These biodegradable polymers enable gradual replacement of the scaffold by the cells from the graft and the host. In addition to providing mechanical support to the forming tissue, some synthetic scaffolds can provide instructive signals to nearby cells. Furthermore, scaffolds specifically tailored to patients can be fabricated by using computed tomography and magnetic resonance imaging, to create 3D images of replacement tissues based on the patient's body. Although the mechanical functions of synthetic scaffolds are extremely useful for building tissues, they can have severe side effects, such as inflammation, scarring and infection. Self-assembly is another line of recapitulating organ and tissue research, in which new tissues are engineered without a scaffold. This involves the use of cell sheet technology, in which successive sheets of cells are added to a special substrate, which allows cell-to-cell adhesion and signalling. This self-assembly of organ components could be especially powerful for the construction of organs with complex structures, such as lung alveoli and kidney nephrons.

Integrating grafts with the host via vascularisation and innervation. To vascularise engineered tissues, the body's own processes can be exploited by introducing growth factors that trigger the development of new blood vessels. Growth factor proteins can stimulate cellular processes including cell proliferation, migration and differentiation during development and tissue healing. Several growth factors have been identified, although their use is limited by their effectiveness, depending on their method of delivery and their short half-life *in vivo*. Using a sequence of growth factors to initiate and then promote the maturation of newly formed vessels can yield more functional networks by mimicking natural development. Another approach to promote graft

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vascularisation is to prevascularise the graft or target site before implantation. Endothelial cells are a flat cell type that forms a sheet, the endothelium, lining all blood vessels. Endothelial cells and their progenitors can self-organise into vascular networks when transplanted on an appropriate scaffold. Combining endothelial cells with tissue-specific cells on a scaffold pre-transplantation can yield tissues that are better vascularised and possess tissue-specific function.

Innervation by the host is also necessary to achieve proper function and full integration of engineered tissues, and may be induced by growth factors. Hydrogels patterned with channels loaded with growth factors and extracellular components can be used to guide nerve growth following implantation, and have been employed to regenerate nerves.

Altering the host environment through cell infusion or modulating the immune system. Therapeutic responses can be induced by indirect means, such as through the secretion of growth factors and interaction with host cells, without the need for consistently transplanting a substantial number of cells into the host. Such examples include the infusion of human umbilical cord blood cells to aid in stroke recovery by stimulating blood vessel growth. This approach is limited however, as cells delivered by this method are often rapidly cleared by the body. However, disguising them from the immune system by encapsulation in hydrogel or coating them with targeting antibodies and peptides can increase residency time at the target site.

The immune system plays a major role in tissue regeneration and can either impair or contribute to the healing process. Engineering the immune system has shown promise in increasing the tolerance to grafts derived from non-host sources, for example by manipulating the responses of immune cells, such as regulatory T cells (cells integral to the immune response). Meanwhile, cellular immunotherapies have potential in tackling cancer: T cells can be removed from the body, modified in the laboratory and then returned to the body with newly acquired cancer-fighting capabilities. Reprogramming macrophages (cells involved in the detection, phagocytosis and destruction of bacteria and other harmful organisms), another cellular component of the immune system, is also a possibility in the fight against infectious diseases, for example tuberculosis, caused by *Mycobacterium tuberculosis*. An existing vaccine has proven to be ineffective and the use of antibiotics has led to resistant strains, however a study indicates promise for an alternative vaccine by reprogramming macrophages in the body to recognise and protect against *Mycobacterium tuberculosis*.

Exploitation of existing and new cell sources. All cells with specialised functions are generated from stem cells. They represent potentially inexhaustible sources of cells and research is approaching the clinical use stage. Human embryonic stem cells (hESCs) are pluripotent and have already been used in several clinical trials. Induced pluripotent stem cells (iPSCs) are formed from differentiated somatic cells, such as blood or skin cells, that have been induced to be pluripotent (through exposure to a suitable set of transcription factors). They possess the ability to differentiate into any other type of cell found in the human body. The discovery of iPSCs in 2006 opened up a vast array of possibilities. For example, an interesting new method is xeno-organogenesis, for the generation of transplantable human organs grown from pluripotent stem cells with the help of specially adapted animal embryos.

Anticipatory policy-making

Stem cells and tissue-engineered products are mentioned in EU legal acts on advanced therapy medicinal products (ATMP). The EU legal frame for ATMP is based on Regulation 1394/2007 and Directive 2001/83 relating to medicinal products for human use. Within the European Medicines Agency, the Committee for Advanced Therapies (CAT), evaluates the quality, safety and efficacy of ATMPs for final approval by the Committee for Medicinal Products for Human Use (CHMP).

Regenerative medicine presents several challenges to policy-makers. Firstly, the use of human stem cells poses ethical considerations, regarding both hESCs and iPSCs. While methods using the latter help alleviate the ethical dilemmas posed by the former, iPSCs raise their own set of concerns around their unlimited potential; the pluripotency of iPSCs afford the possibility of use for human cloning, and the development of human germ cells or embryos. Another area of ethical debate is xeno-organogenesis, where human pluripotent stem cells are used in animal embryos. An additional particular hurdle to policy related to RM is the emergence of a flourishing market in unproven 'stem cell' treatments, in the absence of rigorous scientific evidence. Ethical alarms have been raised over patient safety, as well as the potential negative impact that these practices may have on the development of effective therapies – if many marketed treatments are unsafe or useless – leading to loss of public and investor faith.